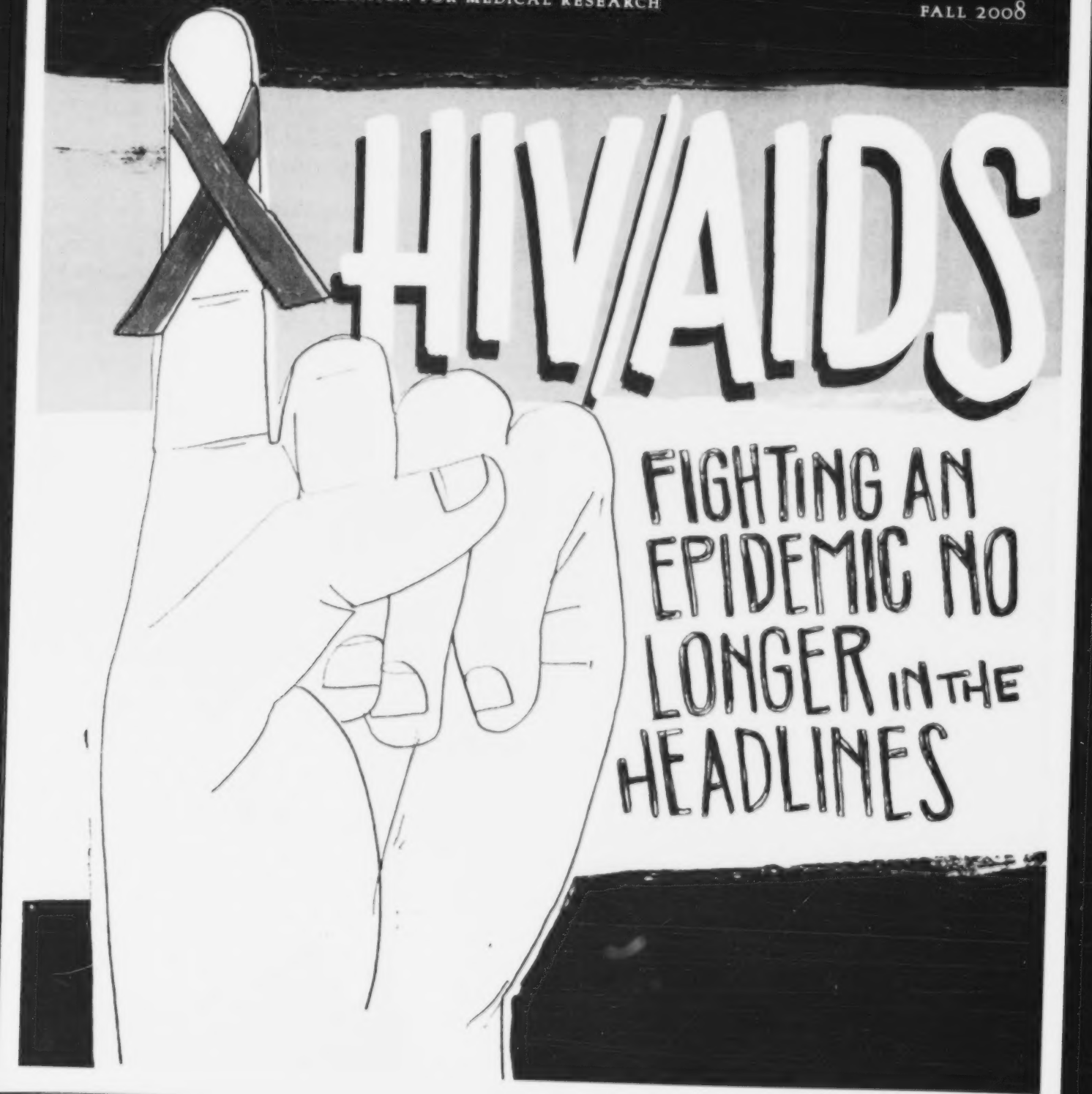
KNEE REPLACEMENT | AHFMR POLARIS AWARD | EPILEPSY

Research News

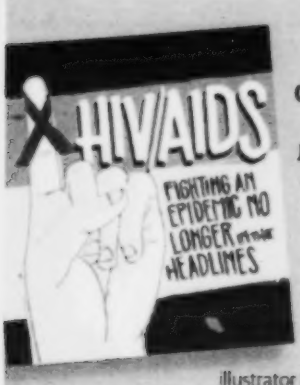
ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

FALL 2008



HIV/AIDS

FIGHTING AN EPIDEMIC NO LONGER IN THE HEADLINES



On the cover

Jeff Kulak completed a Bachelor of Arts in Art and Design at the University of Alberta and now works as a graphic designer and illustrator based in Montreal. His clients include theatre and film companies, art galleries, musicians, and print publications.

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AHFMR MISSION

AHFMR supports a community of researchers who generate knowledge, the application of which improves the health and quality of life of Albertans and people throughout the world. AHFMR's long-term commitment is to fund health research based on international standards of excellence and carried out by new and established investigators and researchers in training.

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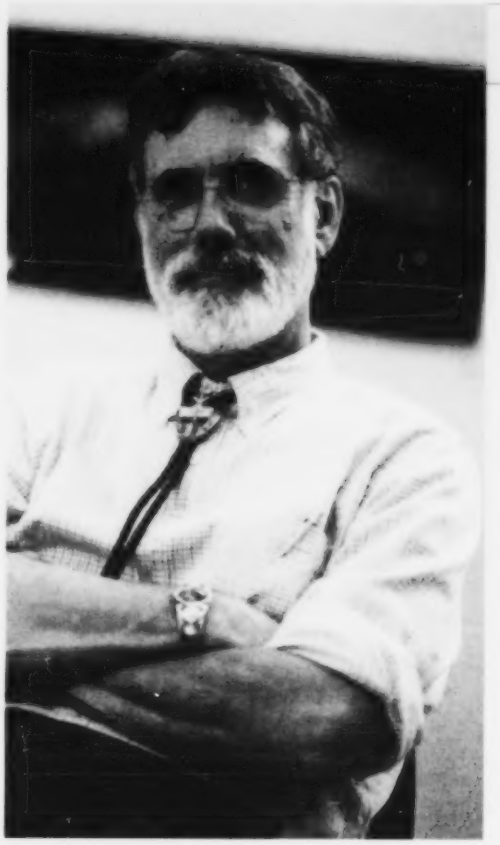

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Dear reader

Missing something?

As a *Research News* subscriber you used to receive a copy of the AHFMR annual report along with your AHFMR calendar. This year we're trying something different. We published our annual report in electronic form in order to use less paper and make less of a dent in the environment.

You can check out the 2008 Annual Report on our website at **www.ahfmr.ab.ca** for information on AHFMR's investment in health research and photos and stories about some of the researchers we support.

Please tell us what you think of our new "paperless" report by filling out a short survey. The survey can be accessed online at www.ahfmr.ab.ca by clicking on "AHFMR's Annual Report Survey". We appreciate your time and value your feedback—complete the survey by December 31, 2008 and we will enter your name in a draw for a cool prize!

Thank you

Our thanks to ***Research News*** readers for participating in our recent readership survey. Your responses will help improve the quality of the magazine for all of our readers.

Congratulations to the survey participants whose names were drawn to receive prizes:

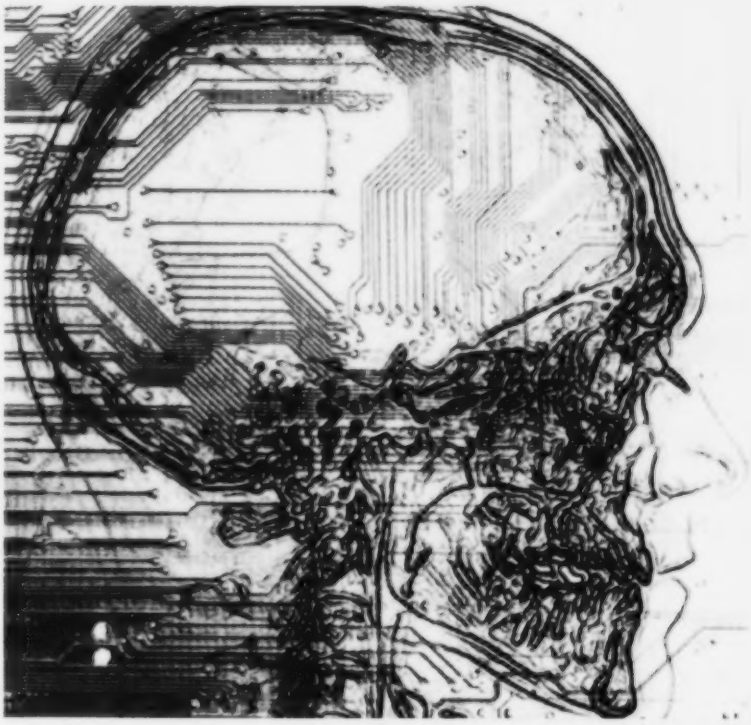
Pandora Lam, Edmonton, Alberta
Blake Williams, Sherwood Park, Alberta

Building scientific infrastructure

Why would a "superstar" neuroscientist like Dr. Bruce McNaughton leave his successful research lab at the University of Arizona to move to Lethbridge? Maybe it's the allure of the multimillion-dollar AHFMR Polaris Award and a province that knows how to support the pursuit of scientific knowledge.

STORY BY JANET HARVEY / PHOTOS BY BERNIE WIRZBA AND VEER

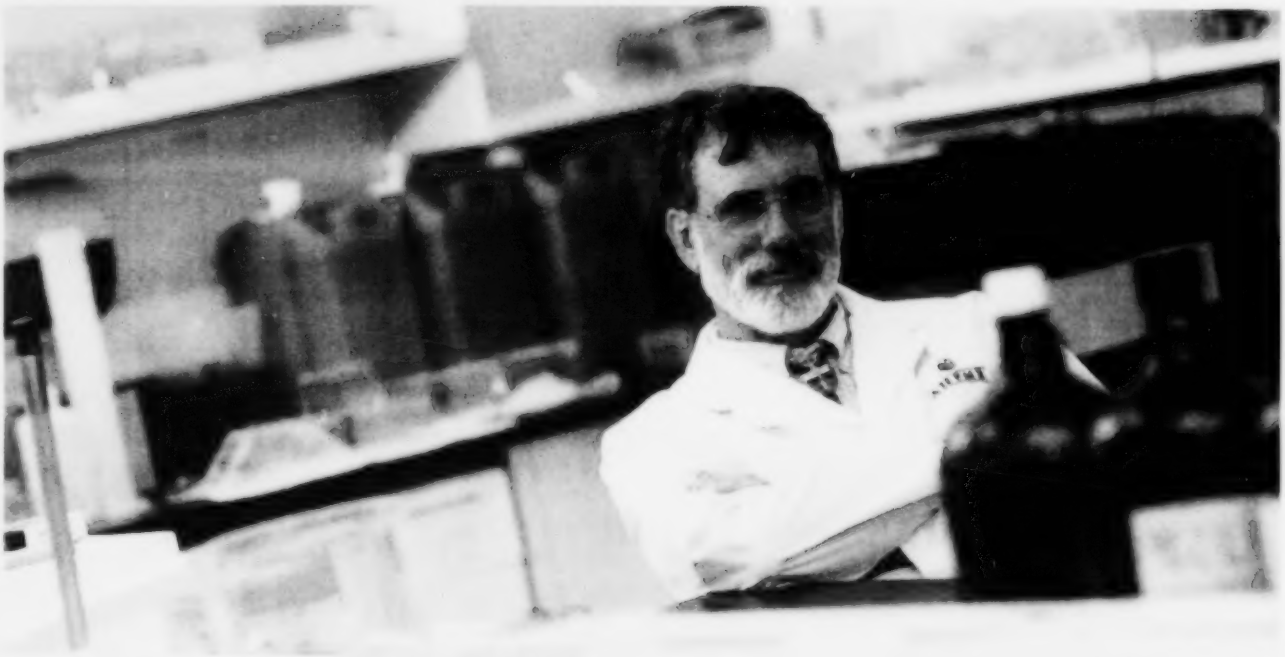
ALBERTA IS SOMETHING OF A MAGNET FOR HEALTH RESEARCH. So says Dr. Bruce McNaughton, a world-renowned neuroscientist and the winner of the first AHFMR Polaris Award. And he should know. In accepting his award, he is moving to the province to set up his lab at the Canadian Centre for Behavioural Neuroscience (CCBN), part of the University of Lethbridge.



"This is the most visionary award developed in North America," he says of the ten-year, $10-million AHFMR Polaris Award, which—together with the required matching funding provided by the University of Lethbridge and iCORE*—is in actuality worth more than $20 million. "I know of nothing else like it."

To Dr. McNaughton, Alberta is a port in the storm that is the research-funding crisis in the United States and, to some degree, in other parts of Canada. The award will enable him to build a team of experts looking at various aspects of how the brain computes and generates knowledge. Some of these experts are already lining up to follow Dr. McNaughton to Lethbridge: negotiations are in progress to bring four more researchers to the CCBN. "These people will bring immense technical skills and modern technologies that will enable us to interact and build knowledge," says Dr. McNaughton. "The AHFMR Polaris Award presents a

*iCORE is the Informatics Circle of Research Excellence



> "This is the most visionary award developed in North America"

Dr. Bruce McNaughton

unique opportunity. Within a few years this centre could be recognized as a mecca for this kind of research."

The kind of research to which he refers is the study of learning and memory; more specifically, how the brain constructs internal representations of the world. He explains that the brain is a dynamic system composed of a huge number of processors that continuously interact with each other "The brain creates its own reality. Everything that comes in is processed against its internal constructs."

Dr. McNaughton's research will build on the groundwork that has already been laid at the CCBN. "People like Dr. Bryan Kolb, Dr. Ian Whishaw, and Dr. Rob Sutherland have created a centre of world-class expertise in behavioural neuroscience here. My contribution will be a focus on the brain's processing elements." Dr. McNaughton's claim to fame is the development of the most advanced technology in the world for studying groups of brain cells and how they interact. This interaction is called *computational neuroscience*: how the brain extracts knowledge from experience.

Dr. McNaughton's work could have important implications for people with brain injuries and age-related brain disorders. "I have worked for many years in the field of aging of the brain. There are increasing possibilities of spinoffs from this work in terms of clinical treatments. And simply understanding the difference between normal and pathological aging gives clinicians a better picture. Not everyone will get Alzheimer's; and just because somebody is getting older does not mean that their memory will be impaired."

But he is also quick to caution about the danger of looking to

science for applications. "There is increasing pressure on scientists in all disciplines to come up with applications for their work. This is a fundamental error on the part of public administrators; and it is unfortunate because it leads to the diversion of people away from basic science. Some scientists are pushed into the position of having to come up with some sort of quick solution from their work. But science works from a large number of people generating knowledge. From that knowledge emerges, now and again, a solution. If you don't foster that infrastructure you will not come up with solutions to health issues and medical problems. We need an infrastructure of people doing science for its own sake, always mindful of its relevance to solving problems." He points out that Alberta has the advantage of being a relatively small, closely knit scientific community—optimal conditions for creating such an infrastructure.

"We need an infrastructure of people doing science for its own sake"

The AHFMR Polaris Award was specifically designed to recruit a "superstar" health researcher to Alberta. The term elicits a grimace from Dr. McNaughton. "My initial reaction to that word is 'Yuck!'—but really, I am delighted to be called a superstar. Superstars in athletics and the arts inspire young people. Scientists don't often get that kind of recognition; and I'd be just as happy not to have it, but it is now increasingly important for young people to be attracted to science. There is a tremendous need for science, and therefore science needs public recognition." ✲

About the researcher

Dr. Bruce McNaughton is the winner of the AHFMR Polaris Award. He is a professor at the Canadian Centre for Behavioural Neuroscience at the University of Lethbridge.

Recommended websites

AHFMR Polaris Award
http://www.ahfmr.ab.ca/press/2007-02-14.php

Canadian Centre for Behavioural Neuroscience
http://ccbn.uleth.ca

iCORE
http://www.icore.ca

A world-class team

Dr. Bruce McNaughton and the other experts he hopes to bring with him to the University of Lethbridge will be joining an established team that is already world-class in its field. That field is *behavioural neuroscience*—the study of the relationship between brain function and behaviour, conducted mainly by observing animals. In this type of research, The Canadian Centre for Behavioural Neuroscience (CCBN) has put Lethbridge on the map as a centre of expertise with an international reputation.

The CCBN team includes

Dr. Rob Sutherland, an AHFMR Scientist who researches *learning and memory*—both normal and disordered. His work could lead to treatments for the memory disorders that come with aging, brain injury, prenatal exposure to alcohol, and neurological disease.

Dr. Bryan Kolb, who studies the largest part of the brain, the ***cerebral cortex***, which controls thought, reasoning, memory, sensation, and movement. He investigates how this part of the brain is organized in mammals and how its organization changes in line with experience. His work has the potential to help people who are recovering after stroke.

Dr. Ian Whishaw, who researches the regions of the brain that initiate and control skilled limb movements, such as reaching for objects and manipulating them. His work could ultimately help people who have suffered brain damage.

Are glutathione supplements effective?

AHFMR researcher Dr. Elaine Leslie provides some answers.

STORY BY CONNIE BRYSON / ILLUSTRATION BY GENEVIEVE SIMMS

About this feature

AHFMR frequently receives letters requesting information about Heritage research or about various medical conditions. "Responding to the reader" is a *Research News* feature intended to provide up-to-date information related to readers' questions, with the help of experts in the Alberta research community. AHFMR cannot provide medical advice, however; please consult your family physician about your specific health concerns.

YOU DON'T HAVE TO LOOK VERY HARD for websites that tout the benefits of taking glutathione as a dietary supplement. If you believe the hype, glutathione supplements can slow down aging, help you lose weight, lower blood pressure, and treat a host of conditions including infertility, cancer, cataracts, and Alzheimer's disease.

Time for a reality check, says AHFMR Scholar Dr. Elaine Leslie, who does research on glutathione at the University of Alberta. While she agrees that glutathione is a very important molecule—it is found in all our cells, where it acts as a mop for neutralizing toxins—there's a catch when it comes to glutathione supplementation. "We have a lot of glutathione in our cells; our cells can synthesize it, and there's no need for more," she says. "And besides, glutathione that we eat is not absorbed well across the digestive tract."

Dr. Leslie notes, however, that in certain situations the stores of glutathione in our cells become depleted. This happens, for example, in one of the most common poisonings worldwide: acetaminophen (e.g., Tylenol) overdose. In such cases, patients are treated with a form of glutathione that is more easily absorbed than

> Glutathione acts as a mop for neutralizing toxins

glutathione itself, allowing its production to return to normal.

In her research, Dr. Leslie studies how toxins are processed in, and removed from, cells. Her major interest is arsenic, a heavy metal that occurs naturally in soil. It can be found in high concentrations in tailings, the materials left over after mining certain ores, including gold. Arsenic causes many problems associated with groundwater contamination, especially in developing nations. Worldwide, millions of people are exposed to concentrations of arsenic in drinking water that exceed the World Health Organization standard.

Glutathione and arsenic form a compound that is more easily excreted from cells than arsenic on its own. But it's not known exactly how this happens. In her post-doctoral research, Dr. Leslie identified an enzyme that is involved in the formation of the compound, and some of her current research follows up on this finding.

"Right now this is basic research," says Dr. Leslie. "We still need to understand exactly how arsenic interacts with glutathione and enzymes. But if we find that a certain enzyme is key to the formation of the arsenic-glutathione compound, this could be a route to making detoxification happen more quickly."

Genetic differences in the production of the enzyme could make some people more susceptible to arsenic poisoning than others. Further knowledge on this subject could be very important in the field of cancer treatment: Arsenic trioxide is used in some types of chemotherapies. Early identification of patients who are particularly susceptible to arsenic toxicity would allow physicians to choose a different treatment. ✲

About the researcher
AHFMR Scholar **Dr. Elaine Leslie** is an assistant professor in the Department of Physiology and the Department of Laboratory Medicine and Pathology, both within the Faculty of Medicine and Dentistry at the University of Alberta.

The study of membranes

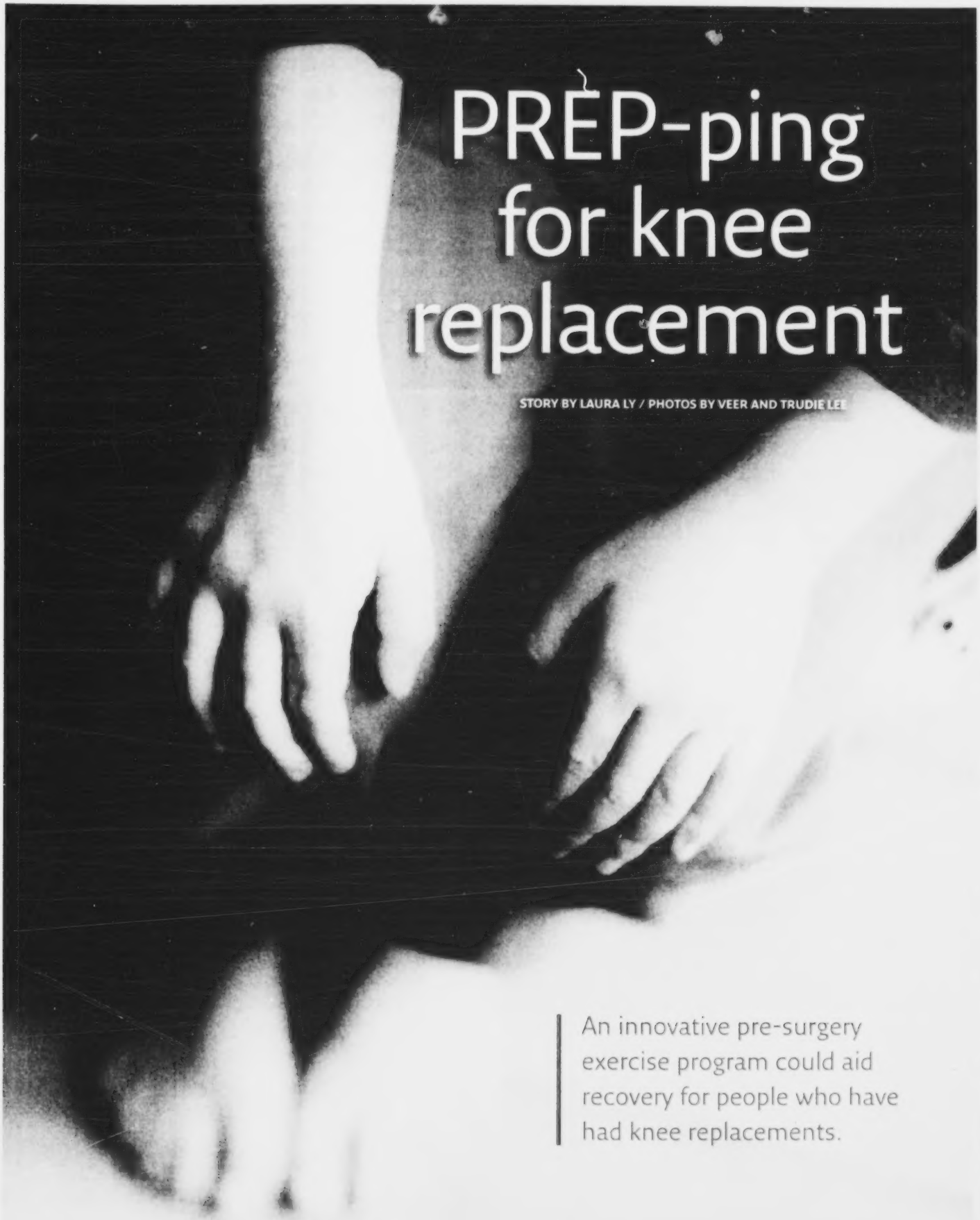
Dr. Elaine Leslie is a member of a large group of researchers at the University of Alberta who share an interest in ***membranes***—the borders that enclose cells. Established in 1991, the Membrane Protein Research Group now has 13 faculty members, 30 graduate students, 13 postdoctoral fellows, and 18 technicians and research associates.

Why study membranes? To the group's director, AHFMR Scientist Dr. Joe Casey, the answer is obvious: "Membranes are the dividing line between life and death. Life goes on inside the cell; there's no life outside the cell. Membranes control what goes into the cell and what comes out of it, they also pass information into the cell."

The group investigates transporters of different molecules and ions across membranes, protein movements across membranes, protein folding, and the role of membrane-associated proteins in controlling cell growth and cellular communication. Their research has implications for a wide range of conditions, including heart disease, cancer, eye diseases, kidney diseases, cystic fibrosis, muscular dystrophy, and Alzheimer's disease.

"And that's just a sampling," notes Dr. Casey. "The list is so long because any dysfunction in membrane structure or function has serious consequences for the normal functioning of cells and can lead to disease." ✲

AHFMR Scientist **Dr. Joe Casey** is a full professor in the departments of Physiology and Biochemistry, part of the Faculty of Medicine and Dentistry at the University of Alberta.



PREP-ping for knee replacement

STORY BY LAURA LY / PHOTOS BY VEER AND TRUDIE LEE

An innovative pre-surgery exercise program could aid recovery for people who have had knee replacements.

TOTAL KNEE-REPLACEMENT SURGERY is an option for patients with arthritic pain and mobility problems; in particular, people suffering from end-stage osteoarthritis. After surgery, patients undergo rehabilitation to regain knee mobility and strength. But what happens when patients with severely limited knee mobility undergo rehabilitation *before* surgery? AHFMR Population Health Investigator Dr. Allyson Jones aims to find out.

Dr. Jones is the principal investigator of the Preoperative Rehabilitation Exercise Program, aptly known as the PREP study. She explains, "With earlier studies, we found that patients' activity level or functional level prior to surgery predicted how well they recovered six months after total knee-replacement surgery. Based on that work, we want to see if we can maintain or improve a patient's functional level while they wait for surgery." *Functional level* is measured by a person's ability to perform basic daily activities such as walking and climbing stairs.

The program is designed for a particular subgroup of patients undergoing knee replacements: those with the lowest functional level and the most difficulty with pain. Participants in the study will be randomly divided into two groups. Members of one group will be assigned a home exercise program, administered by a physiotherapist, for eight weeks prior to surgery. The program will work on managing pain, increasing strength and overall mobility, and extending range of motion in the knee. At week four the physiotherapist will measure progress and adjust the exercise program accordingly. In the other group, members will prepare for surgery without this exercise program. "Patients in both groups will have a physiotherapist phone them on a weekly basis to see how they are managing," says Dr. Jones.

What happens when patients undergo rehabilitation before surgery?

Participants are currently being recruited through the Alberta Hip and Knee Clinic in Edmonton; 230 patients will be involved. "We are recruiting patients as they are seen by the orthopedic surgeon. We assess them nine to ten weeks before surgery, and again before hospital admission when the exercise group have completed their program. Then we follow them up at one, three, and six months post-operatively," Dr. Jones explains. During the follow-up assessments, patients will answer questions about their pain, their mobility, and their overall health status. They will also be asked to perform knee and arm exercises to measure their range of motion, muscle strength, and agility.

Epidemiologists, rheumatologists, orthopedic surgeons, health economists, and pharmacists are also involved in the study. As Dr. Jones explains, research projects in the area of clinical rehabilitation often involve multidisciplinary teams. "It's all part and parcel with the type of research we are doing. It's a great team effort."

A future related study may target patients who are waiting for knee replacements but who have a higher level of function than those involved in the

Quick Facts

What is total knee replacement?

Total knee-replacement surgery involves replacing the damaged knee with an artificial version made of metal and plastic. The bottom end of the thigh bone and the top end of the shin bone are replaced, and often the back of the kneecap is refaced.

"'Pre-habilitation' in the form of exercise may improve overall health"

first PREP study. "We want to evaluate patients waiting for their surgery who, while still having functional limitations, can perform a more aggressive exercise program."

Ultimately, Dr. Jones and her colleagues want to develop a preoperative exercise program that will be the most beneficial to the recovery of patients with knee replacements. Dr. Jones says that "it's often a challenge to rehabilitate patients who have had total knee replacements. Helping patients regain joint mobility and strength, and return to regular activity involves a lot of work during the post-operative period. Basically, we want to identify optimal exercise programs for patients while they wait for surgery."

Dr. Jones argues that pre-surgery rehabilitation may be beneficial not only for knee function and the recovery process, but also to overall health and quality of life for patients. "Pain is typically the primary reason for having a knee replacement. Because of the pain, patients are less active. 'Pre-habilitation' in the form of exercise may improve overall health because it may maintain—or even increase—activity during the period when patients are waiting for their surgery." ❋

About the researcher

AHFMR Population Health Investigator **Dr. Allyson Jones** is an associate professor in the Department of Physical Therapy, part of the Faculty of Rehabilitation Medicine at the University of Alberta. She also has a cross appointment in the Department of Public Health Sciences, and is a member of AHFMR's interdisciplinary team in bone and joint health.

Selected publication

Jones CA, Beaupre LA, Johnston DWC, Suarez-Almazor ME. Total joint arthroplasties: current concepts of patient outcomes after surgery. *Rheumatic Disease Clinics of North America*. 2007 Feb;33(1):71-86.

Recommended websites

Alberta Bone and Joint Health Institute:
http://www.albertaboneandjoint.com/

Alberta Osteoarthritis Team:
http://www.albertaosteoarthritisteam.ca/

RESEARCH THAT HITS HOME

> Neuroscientist Dr. Michael Colicos has studied epilepsy for almost twenty years. But when the disorder was diagnosed in his infant daughter, his research took on new meaning. <

STORY BY JANET HARVEY / PHOTOS BY TRUDIE LEE A EL COLICOS

When Alexandra Colicos experienced her first epileptic seizure at the age of nine months, her father understood better than most what was happening to his little girl: AHFMR Scholar Dr. Michael Colicos studies nerve-cell connections in the brain. During the 15 years prior to his daughter's diagnosis, he had been examining how these connections change when we learn and remember things, and how they go wrong in conditions such as epilepsy and autism.

Suddenly he had a much more personal interest in what was happening in those cells during epileptic seizure. "It's very strange. On one hand, I'm a neuroscientist, fascinated with what the brain is doing," he says. "But on the other, I'm her father, and it's my little girl that is having a seizure." Dr. Colicos, an avid photographer, has used his camera to document much of Alexandra's painful and exhausting journey, including her treatments.

> "Neurons in the brain are constantly communicating"

While aspects of the situation are heartrending, his dual role gives Dr. Colicos a new perspective on the disorders he studies. And the technology he has developed gives him new insights. He uses *photoconductive stimulation* to work with networks of brain cells (neurons) and to make live movies of their activity. This tool, created by growing the nerve cells on silicon chips, allows researchers to observe the cells in great detail and with great clarity. "Neurons in the brain are very dynamic," says Dr. Colicos. "They're constantly communicating and looking for new connections with other neurons."

His technology provides dramatic illustrations of this constant activity. Nerve cells in normal networks flash one after another in seemingly random locations, like stars twinkling in a night sky. Cells that have genes associated with autism flash on and off in a smooth wave that seems to move across the neural network. And cells in a state of induced seizure go off like an explosion: all the cells fire very fast—like the night sky suddenly burning out. And some of them do in fact die.

Quick Facts

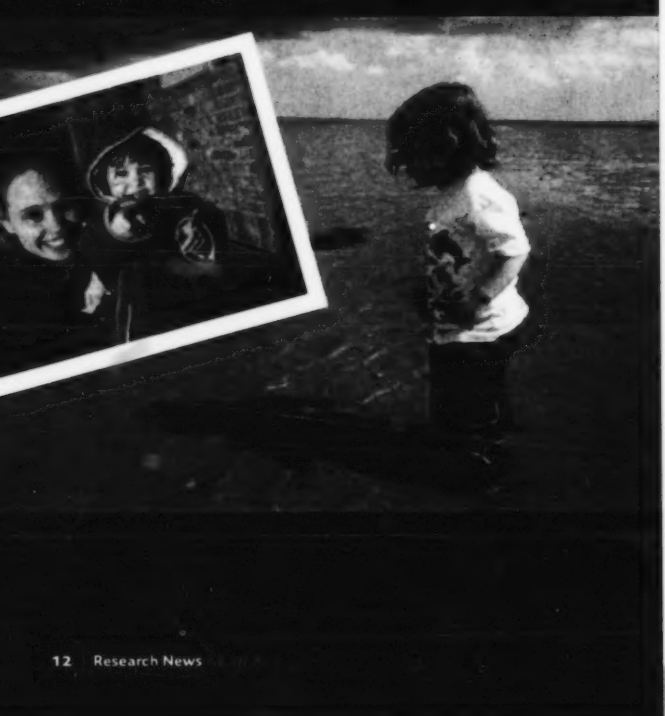
What is epilepsy?

Epilepsy is a neurological disorder characterized by sudden, recurrent seizures. A seizure is caused by a temporary change in the brain's electrical functioning. The disorder affects approximately 50 million people worldwide, including about 200,000 in Canada. There is no cure for epilepsy, but long-term drug therapy can reduce the frequency and severity of seizures. In some cases when medication fails, surgery is recommended. In about 50% of childhood cases of epilepsy, seizures disappear as the child grows older.

Sources

Epilepsy Canada • http://www.epilepsy.ca
Epilepsy.com • http://www.epilepsy.com

Left: Dr. Michael Colicos and wife Robyn Flynn with their daughter Alexandra



> Alexandra might simply outgrow her condition

"Now that we can directly observe how these neurons behave in real time, we need to figure out why this happens," says Dr. Colicos. "Why do cells communicate differently in these disorders?"

Photoconductive stimulation has a great deal of potential for helping to answer this question—and others. For example, it can be used to test drugs such as anti-epileptic therapies: researchers can see their effect on nerve cells in great detail. It provides an alternative to testing drugs on live animals, because researchers can take the brain cells from one rat and make hundreds of these chips. And it can be used to test new therapeutic approaches for other medical conditions, such as stroke and spinal cord injury.

Dr. Colicos uses the technology to study the neuron connections involved in learning and memory. "If you stimulate a cell repeatedly, it forms new connections," he explains. "These connections between your neurons change the way you think—which is what occurs when you

Quick Facts

What is autism?

Autism is a disorder involving the development of the nervous system. Some of the best-known symptoms are delays in language development; difficulties in understanding and participating in social relationships; and preoccupations with repetitive tasks or behaviours. Autism is thought to develop in the womb; however, children with the disorder often seem typical in their first few months. One out of every 150 children in Canada has autism.

Source

AHFMR *Research News*, Spring 2008

learn or remember something. In the brain, all of the neurons work at the same time. While your laptop might have a dual-core processor, the brain has close to a trillion cores working together. This is how the incredible information-processing abilities of the brain arise."

So what does this knowledge of how brain cells connect mean for little Alexandra? Even the most innovative and groundbreaking research can take years to evolve into a treatment that can be used in the clinic. Dr. Colicos's studies could have an impact on future treatments for epilepsy and other disorders, but such possibilities are a still a long way off. For now, Alexandra's best hope is that she might simply outgrow her condition; that happens in about half of all cases of childhood epilepsy. Now two-and-a-half years old, she has seizures that occur in clusters. Over a period of days, they can be as frequent as every hour; but the cluster can be followed by months without any problems.

"As a parent, I find it very hard to see her go through this," says Dr. Colicos. "But it helps that the people treating my daughter are colleagues of mine who also research epilepsy. I know first-hand that she's getting the best care and that we're all working to better understand her disorder." ❊

About the researcher

Dr. Michael Colicos is an *AHFMR Scholar* and an assistant professor in the Department of Physiology and Biophysics, part of the Faculty of Medicine at the University of Calgary. He is also a member of the Hotchkiss Brain Institute there.

Selected publication

Goda Y, Colicos MA. Photoconductive stimulation of neurons cultured on silicon wafers. *Nature Protocols*. 2006;1(1):461-467.

Recommended websites

Dr. Michael Colicos's website

http://www.ucalgary.ca/colicos

Homemade technology

In 2001, while he was a post-doctoral fellow with Dr. Yukiko Goda at the University of California, San Diego, Dr. Michael Colicos developed a technology called photoconductive stimulation, which allows him to target specific neurons in a living network of brain cells and fire them. Using brain cells cultured from rats, he grows the networks on wafers made of silicon—an element that, because it conducts electricity, is often used in the manufacture of computers and other electronic equipment. He then uses a laser to shine light on the silicon, thereby causing changes in the conductivity. Because electricity flows through silicon most easily where the light shines, that's where most of the current runs. That current causes the cell to fire. Dr. Colicos can then observe how nerve cells respond: how they change their connections with one another. This process is similar to what happens in our own brain when we learn and remember things.

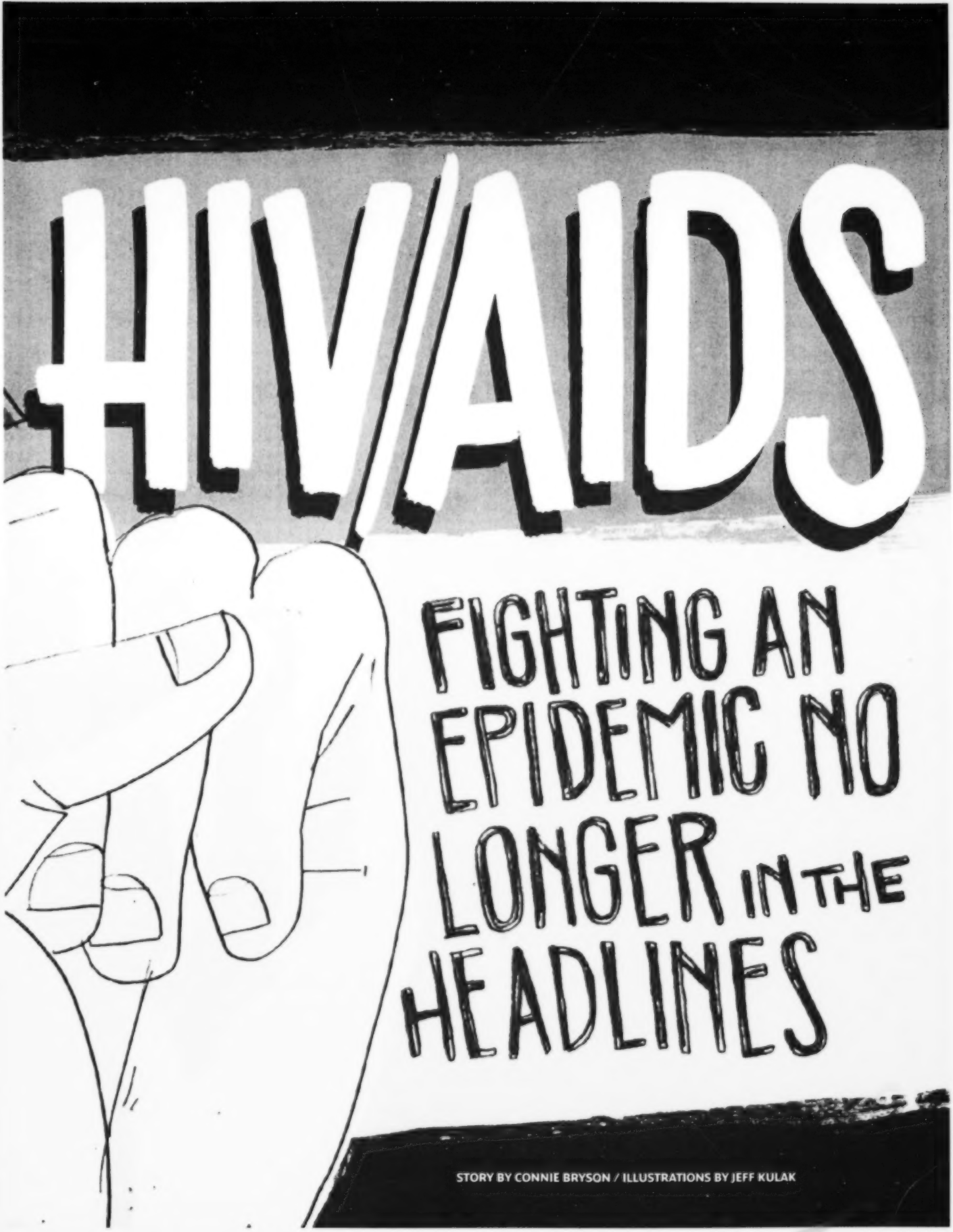
Dr. Colicos's groundbreaking technology was built, as he puts it, from things you find around the house or the lab: old CD players, Petri dishes, laser pointers, bits of plastic, and the like. It took him six months and five different versions to get everything just right. In fact, a couple of the early prototypes blew up and caught fire, he relates with a grin. His goal now is to use the technology he has developed to study neurological disorders. "The next generation [of the device] will be more advanced. It will be able to index millions of points simultaneously, and stimulate a large number of cells at the same time at different frequencies and rates." ❊

HIV and AIDS have fallen off the public's radar to some extent. Highly effective new drugs mean that AIDS is no longer a death sentence. But there is still no cure, and the disease continues to affect millions of people around the world—in epidemic proportions.

SINCE THE EARLY 1980S, when acquired immune deficiency syndrome (AIDS) was identified and attributed to the human immunodeficiency virus (HIV), the virus has rocketed to its current standing as the number one infectious cause of death in the world. In the countries hit hardest by HIV, it is *the* most important health problem. In southern Uganda, for example, AIDS is the cause of 80% of adult deaths. But even in Alberta, where infection rates are much lower, HIV/AIDS is a serious issue. It's estimated that there are close to 3,000 Albertans living with HIV, which remains a deadly transmissible virus.

"If you're looking for the answer to 'Why do HIV/AIDS research?', the numbers speak for themselves," says Dr. Stan Houston, director of the Northern Alberta HIV Program and a professor at the University of Alberta. "While there have been two major successes in HIV research to date—a reliable test for the virus and an effective therapy for those who can organize their life in such a way as to take the treatment—there is still no cure. And a vaccine for HIV has remained elusive.

"The other striking characteristic about HIV is how it interacts dramatically with social, cultural, and economic factors in ways we only partly understand. Because HIV intersects with so many sensitive issues—sex, drug use, death—what you might think is strictly a health issue is greatly complicated by the political and social response to it. This has been true of AIDS from the beginning, when it was thought to be a disease of only gay men and Haitians. Now we're seeing some of the HIV/AIDS research agenda devoted to investigating these social issues.



STORY BY CONNIE BRYSON / ILLUSTRATIONS BY JEFF KULAK

"And active research on many fronts means there's another aspect to HIV and AIDS—things change so fast that there is always something to keep you on your toes."

HIV around the world: the numbers

An estimated 33.2 million people around the world were living with HIV in 2007. In the same year, an estimated 2.5 million people became newly infected with HIV, and an estimated 2.1 million people died of AIDS-related causes.

AIDS was first diagnosed in 1981. Canada saw its first case of AIDS in 1982, and the first Canadian death attributed to AIDS the year after that. Approximately 21,000 people in Canada have since died while infected with HIV. At the end of 2005, an estimated 58,000 people were living with HIV infection (including full-blown AIDS); this number signalled an increase of about 16% from 2002 figures. Health Canada estimates that 27% of people living with HIV in 2005 were as yet unaware of their status.

Sources: Joint United Nations Programme on HIV/AIDS, World Health Organization, Public Health Agency of Canada

STUDYING THE COMPLICATIONS

■ In 1982, while he was working as a resident in internal medicine, AHFMR Senior Scholar Dr. Chris Mody cared for the first AIDS patient in Calgary. "In those days, AIDS was very mysterious and very scary. We didn't even know it was a viral disease. Caring for this patient was a profound experience that marked an important point in my career. It got me thinking: Why is it that some people are infected with certain microbes and others are not?"

The question led Dr. Mody to study the defence mechanisms of hosts such as humans—how to manipulate these defences to our advantage, and how to restore them to full functionality when they are defective. His research team investigates the immunological response to infections in patients whose immune systems are weakened, such as those with cystic fibrosis and AIDS. One of the hallmarks of HIV infection is that it leaves people vulnerable to opportunistic infections from other viruses, as well as bacteria and fungi.

At the University of Calgary, Dr. Mody studies a particular fungus called *Cryptococcus neoformans*. It usually does not cause disease in healthy people, but it often causes meningitis and pneumonia in AIDS patients. Dr. Mody has begun to explore how the immune system protects against organisms that can cause disease. It turns out that different types of white

Quick Facts

HIV is a ***retrovirus***. This type of virus spreads by inserting itself into a host's cells and taking over the cells' self-reproduction mechanism to make copies of itself.

blood cells use different mechanisms. The T cells, for example, use a protein called granulysin to kill pathogens; the NK cells use one called perforin. "The interesting thing about this is that both kinds of cells have access to both killing proteins, yet each kind chooses to deploy only one," says Dr. Mody. "The natural follow-up to this observation is: Can we exploit the other mechanism when the first one is exhausted?"

Dr. Mody's team found that the mechanism that triggers T cells to make granulysin is defective in patients who are infected with HIV. "We are trying to figure out whether we can overcome this defect and restore the response of the T cells. And if we can get them to make granulysin, we will have to determine whether that protein is effective. This could be the key to improving the immune response of people with AIDS."

About the researcher

AHFMR Senior Scholar **Dr. Chris Mody** is a full professor in the Division of Pulmonary Medicine, part of the Department of Medicine at the University of Calgary.

Selected publication

Zheng CF, Ma LL, Jones GJ, Gill MJ, Krensky AM, Kubes P, Mody CH. Cytotoxic CD4+ T cells use granulysin to kill Cryptococcus neoformans, and activation of this pathway is defective in HIV patients. *Blood*. 2007 Mar 1;109(5):2049-2057.

NEUROLOGICAL PROBLEMS

■ NEUROLOGICAL PROBLEMS ARE ANOTHER COMMON COMPLICATION OF HIV INFECTION, because infected cells can easily enter the brain and the peripheral nervous system. In fact, at least 25% of people with HIV infections develop neurological complications. At one time AIDS-related dementia was an almost inevitable consequence of HIV infection. Although antiretroviral therapy has cut the rate of serious dementia, other problems are emerging, notes AHFMR Senior Scholar Dr. Chris Power, an Edmonton neurologist and AIDS researcher at the University of Alberta.

"We've gone from a situation where patients were all dying to a situation where patients have a chronic disease that is horrible, but are living longer and with a better quality of life," he says. "But as they live longer, we're now treating different neurological problems."

One of these problems is nerve damage known as *peripheral neuropathy*. The condition can manifest itself as a feeling of pins and needles, unexplained pain, burning, stiffness, or numbness in the feet and toes. Dr. Power says that severe cases of neuropathy are "exquisitely painful and disruptive to quality of life." Another condition that has emerged with the advent of antiretroviral therapy is *neurological immune reconstitution inflammatory syndrome* (IRIS). This is an autoimmune disease that causes people to get sicker even though the antiretroviral therapy has improved their immune function. It is the subject of a great deal of current research.

In Dr. Power's lab, the focus is on understanding how HIV gets into the brain and damages brain cells. His team has found that HIV activates an enzyme known as MMP-2, which in turn alters a usually beneficial molecule in such a way that it starts killing brain cells. Dr. Power first identified the process in 2003, and has since done a series of studies on MMP-2. "To prevent neural injury, we need to find some way of suppressing the enzyme or blocking the receptor. That's the goal of the research," he says.

Neurological problems are another common complication of HIV infection

"As a physician, I can see the benefits of being able to do this. Right now, we can prevent some of the neurological complications of HIV infection as long as patients begin antiretroviral therapy at an early stage. But for patients who are late presenters to medical care, antiretroviral therapy isn't as effective. And this is a major, growing group of people, especially in sub-Saharan Africa. The bottom line is that we need better medicines and an effective vaccine for HIV."

About the researcher

AHFMR Senior Scholar **Dr. Chris Power** holds a Tier 1 Canada Research Chair in Neurological Infection and Immunity. He is a full professor in the Department of Medicine (Neurology) at the University of Alberta.

Selected publication

Zhang K, McQuibban A, Silva C, Butler GS, Johnston JB, Holden J, Clark-Lewis I, Overall CM, Power C. HIV-induced metalloproteinase processing of the chemokine stromal cell derived factor-1 causes neurodegeneration. *Nature Neuroscience*. 2003 Oct;6(10):1064-1071.

BASIC CELL BIOLOGY

■ For AHFMR Scientist Dr. Richard Wozniak, it's all about the nucleus. "The nucleus is the 'brains' of the cell. It contains the genetic material, and controls the cell by regulating gene expression. In my lab we study *nuclear transport*—the mechanisms by which things get in and out of the nucleus."

While much of Dr. Wozniak's work at the University of Alberta has clear implications for cancer research, a significant part is relevant to the quest for a better understanding of HIV infection. When a virus enters a cell, one of its main targets is the *nuclear transport machinery:* the proteins that control what gets across the membrane of the nucleus. In some cases, viruses just take over the machinery for their own benefit, so that they can get whatever they need into the nucleus. In other cases, such as with HIV, the virus not only usurps the machinery, it interferes with nuclear transport. In turn, this can interfere with the immune response and, therefore, the body's ability to fight off the virus.

But before scientists can understand what goes wrong with nuclear transport in HIV infection, they must know exactly how nuclear transport works. It differs from transport across other types of cell membranes; that's because things don't actually cross a membrane in nuclear transport. The nucleus is surrounded by two membranes that form an envelope. At certain points around the nucleus, the envelope is fused and forms a hole—a bit like the hole in a doughnut. This complex structure, made up of

How does HIV get into the brain and damage brain cells?

HIV interferes with nuclear transport

proteins, is called the *nuclear pore complex* (NPC). The nucleus is dotted with about 5,000 NPCs. They are the gateways in and out of the nucleus.

Viruses target certain proteins in the NPCs, altering the nuclear transport machinery and allowing the virus into the nucleus. One of the things a cell does in response to a virus is to change the composition of the nuclear transport machinery, so as to retain some resistance to the virus.

"This is very complicated," notes Dr. Wozniak. "Because the virus is using the machinery, and because the machinery is part of the response to the virus, we need to know more.

"We're at the initial stages now—the work with viruses represents a new direction for my lab. Most of our effort to date has focused on identifying the molecular players in nuclear transport. As that situation has become clearer, we're starting to look at what the players are doing in response to a virus. In this regard, we are excited about some recent results. We have identified proteins that may play a role in the cellular defence against viruses. In the long term, we may be able to disrupt the virus's ability to control the cell by manipulating nuclear transport."

About the researcher

AHFMR Scientist **Dr. Richard Wozniak** is a full professor in the Department of Cell Biology in the Faculty of Medicine and Dentistry at the University of Alberta.

Selected publication

Makhnevych T, Ptak C, Lusk CP, Aitchison JD, Wozniak RW. The role of karyopherins in the regulated sumoylation of septins. *Journal of Cell Biology*. 2007 Apr 9;177(1):39–49.

EXPLORING THE SOCIAL ISSUES

■ AIDS MAY BE A DISEASE; but to understand its prevention and treatment we have to look beyond basic science and medicine to how it interacts with other aspects of people's lives. This point of view is shared by many AIDS researchers, including Dr. Catherine Worthington, an AHFMR Population Health Investigator from the University of Calgary.

"A disproportionate number of people living with HIV/AIDS are coming from populations such as injection-drug users, Aboriginal people, and street youth," she says. "We don't hear about HIV as much in the media as we used to, but the numbers prove it is still a huge problem."

Dr. Worthington recently concluded a study of HIV and the support services available to street kids in Calgary. Her work grew out of the increasing recognition that social services designed from a middle-class, nine-to-five perspective will probably not meet the needs of other groups. Working with youth organizations, health-service agencies, and young people themselves, the research team identified factors that promote or impede the use of these services. The results are already being used by various agencies in designing services for young people and in educating those who will provide these services. Round-table meetings and community workshops also helped get the results out to the community.

Dr. Worthington recently collaborated on another study about HIV and Aboriginal youth that was national in scope. A clear message coming from community consultations was that young Aboriginals don't know enough about HIV and their own HIV risk. "Part of that is just being young; but another part is being Aboriginal,

"Young people's awareness of HIV has fallen off over the last decade"

from a culture where sexuality is not always easily discussed," says Dr. Worthington. "Young people's awareness of HIV in general has fallen off over the last decade. There is a lot of work to be done in making services more accessible, friendly, appropriate for youth, and for those from distinct cultures."

Another of her collaborative projects—this one involving AIDS Calgary and Dr. David Este from the University of Calgary's Faculty of Social Work—examines HIV/AIDS services to Calgary's communities of African immigrants. Through one-on-one interviews and focus groups, the team has identified service needs and gaps. "In African countries, messages about HIV/AIDS are plastered everywhere on billboards. It's not really visible here. The results [of our research] are telling us we need to integrate HIV services with services to immigrants. We need to get the message out that AIDS is an issue here too."

In the long term, Dr. Worthington plans to extend her community-based research by analyzing the extent to which people living with HIV in Alberta make use of health support services. "By doing this, we would have a better picture of who is going for what types of care, and what the outcomes are. This kind of insight would be of interest not only locally, but nationally as well."

The changing face of AIDS in Canada

The face of HIV/AIDS has changed dramatically in Canada over the past quarter of a century. On its website, the Public Health Agency of Canada says this about HIV/AIDS in Canada:

> Canada's HIV/AIDS epidemic is now actually several epidemics, occurring in specific populations. Although men who have sex with men (gay men and homosexually active men) continue to be the population most affected by HIV/AIDS, the disease has also become a significant public health issue for injecting drug users, women, Aboriginal peoples, prison inmates, people from countries where HIV is endemic, as well as those already living with HIV/AIDS. Risk behaviour data on young Canadians also show significant potential for HIV transmission among youth.

About the researcher
AHFMR Population Health Investigator **Dr. Catherine Worthington** is an associate professor in the Faculty of Social Work at the University of Calgary.

Selected publication
Worthington C, Myers T, O'Brien K, Nixon S, Cockerill R, Bereket T. Rehabilitation professionals and human immunodeficiency virus care: results of a national Canadian survey. *Archives of Physical Medicine and Rehabilitation*. 2008 Jan;89(1):105-113.

Recommended websites
HIV Edmonton
http://www.hivedmonton.com

AIDS Calgary Awareness Association
http://www.aidscalgary.org

QUALITY OF LIFE

■ WITH RESEARCH INTERESTS IN EPIDEMIOLOGY, VULNERABLE POPULATIONS, AND INFECTIOUS DISEASES, Leah Martin found the mentorship she needed in the supervisors for her Ph.D. thesis at the University of Alberta. Dr. Duncan Saunders, current chair of the Department of Public Health Sciences, is an epidemiologist who studies HIV infection in Africa. Dr. Stan Houston is an infectious-disease specialist and director of the Northern Alberta HIV Program. Together these three researchers developed a project to look at the effect of drug therapies on the quality of life of HIV-infected patients in both Northern Alberta and Uganda.

For the Alberta-based part of the research, Martin is studying patients in Edmonton HIV clinics who started "highly active antiretroviral therapy" (HAART) between 1997 and 2005. Martin is assessing three possible outcomes: mortality, treatment failure, and health-related quality of life. Her particular interest is Aboriginal people who are infected with HIV.

"There's evidence from the literature that the outcomes for Aboriginal people on antiretroviral therapy are not as good as for non-Aboriginals," notes Martin. "In general, Aboriginal people have poorer health and lower socioeconomic status compared to the rest of the Canadian population, and these factors may lead to the poorer treatment outcomes. To be successful, antiretroviral treatments require a very high level of adherence [to the treatment regimen], and this can be extremely difficult for people who lead unstable lifestyles, as many injection-drug users do. A large number of the Aboriginal patients in our study have a history of injecting drugs. By looking more carefully at patients' treatment outcomes, we aim to find ways to improve their success on therapy."

"Increasingly, AIDS is the disease of poverty and marginalization and disadvantage"

For the Uganda-based part of the project, Martin is studying data from a rural HIV clinic where antiretroviral therapy has only recently become available. The objective is similar to her work in Alberta: get a better handle on what factors predict successful outcomes. Martin hopes to finish her thesis later this year.

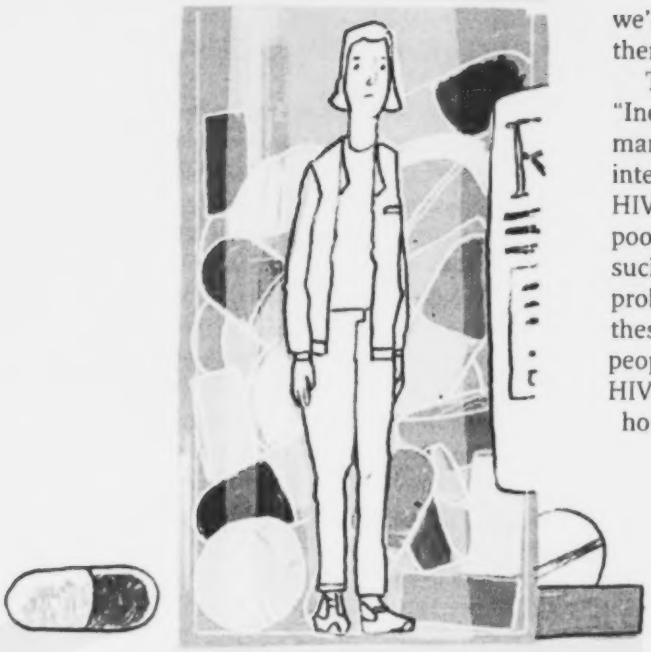
"My Ph.D. research will quantify some important outcomes; for example, we have found that Aboriginal people have higher rates of HIV-related mortality after starting treatment. But there's a lot more qualitative work that needs to be done, too, especially in terms of understanding the treatment experience of Aboriginal people receiving antiretroviral therapy. This understanding will help clinicians improve treatment experiences for these patients and contribute to better outcomes. We need to address these issues if

HIV, AIDS, and HAART

HIV (human immunodeficiency virus) is the virus that causes the disease we call AIDS (acquired immune deficiency syndrome). HIV weakens the immune system by attacking certain white blood cells called T-helper cells. These cells play a central and crucial role in the immune response, and without them the body can't fight off disease. If the numbers of T-helper cells fall below a certain level, the result is AIDS: a chronic, progressive illness that leaves infected people vulnerable to opportunistic infections and cancers. There is no cure for AIDS.

There is, however, effective treatment for HIV infection—in the form of a regimen of three or more drugs, known as HAART (highly active antiretroviral therapy). HAART has significantly decreased the number of AIDS-related deaths. Although it isn't a cure for AIDS, it reduces the amount of virus circulating in the blood to nearly undetectable levels. However, make no mistake: HIV will always be present in the body, and people must stay on HAART for the rest of their lives.

Sources: Health Canada, National Institutes of Health (US), Centres for Disease Control



we're going to be successful with antiretroviral therapy in these vulnerable populations."

That is music to Dr. Houston's ears. "Increasingly, AIDS is the disease of poverty and marginalization and disadvantage, both at the international and local level," he says. "In Canada, HIV infection hits certain groups the hardest—the poorest people and people with social problems such as homelessness and addiction, or clinical problems such as psychiatric illness. We see these people every day in HIV clinics in Alberta: people who are really struggling, not only with HIV but also with poverty, psychiatric illness, homelessness, and drug addiction."

In 1987 Dr. Houston went to Africa to work in the field of tropical diseases; he arrived just as the AIDS epidemic was exploding. Since then, he has devoted his career to caring for AIDS patients and doing HIV research. "Looking after AIDS patients, especially in 2008, is incredibly rewarding. Not only is there potential for spectacular medical benefit with the newer treatments, but often people with really serious personal and lifestyle problems are able to move their lives forward in dramatic ways. You see these changes and it's rewarding to have played a small part in them." ❋

About the researchers

Leah Martin holds an *AHFMR Health Research Studentship* and is a Ph.D. candidate in the School of Public Health at the University of Alberta.

Dr. Stan Houston is a full professor in the Department of Medicine (Infectious Diseases), within the Faculty of Medicine and Dentistry at the University of Alberta. He is also the director of the Northern Alberta HIV Program.

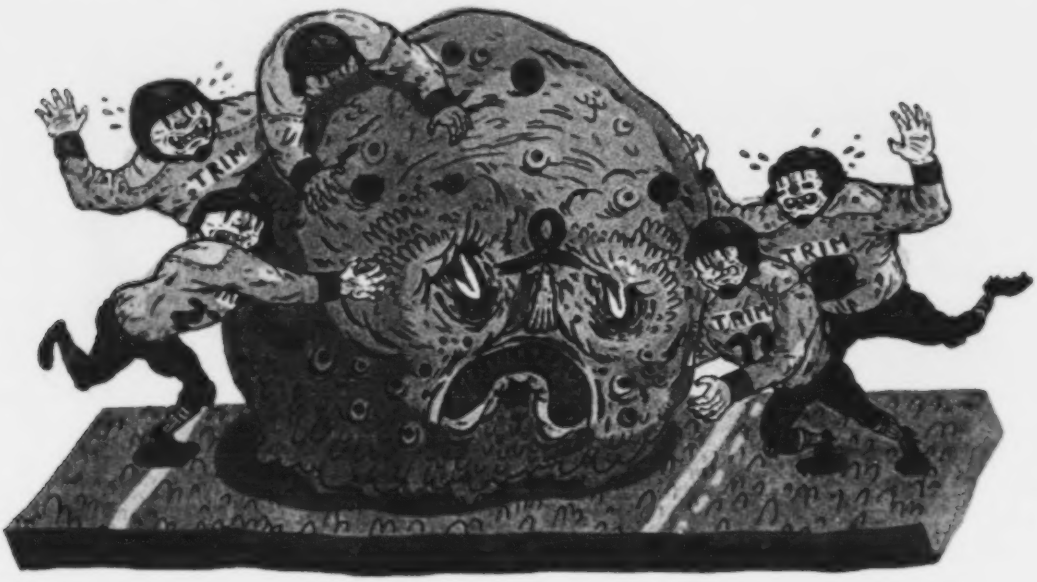
Selected publication

Corbett EL, Muzangwa J, Chaka K, Dauya E, Cheung YB, Munyati SS, Reid A, Hakim J, Chandiwana S, Mason PR, Butterworth AE, Houston S. Nursing and community rates of Mycobacterium tuberculosis infection among students in Harare, Zimbabwe. *Clinical Infectious Diseases*. 2007 Feb 1;44(3):317–323.

New hope in gene therapy

A former AHFMR Fellow has found a gene that may be able to block HIV.

STORY BY TARA NARWANI / ILLUSTRATION BY BRENNAN KELLY



THE HUMAN IMMUNODEFICIENCY VIRUS (HIV), the virus that causes AIDS, is a sneaky biological enemy. It inserts its own genetic material into certain cells that are indispensable to our immune system—after which the virus cannot be removed. Once HIV infects a person, they're infected for life. "In essence, HIV hides in our bodies, so we can't get rid of it completely," explains Calgary-born virologist Dr. Stephen Barr. This makes finding a cure for AIDS a very difficult prospect.

Over the past 20 years, research has answered a lot of questions about how HIV is transmitted and how it infects the body. By contrast, it has revealed very little about how the body naturally defends itself against HIV infection. Identifying key components of our immune response to HIV could yield new forms of drug treatment.

Dr. Barr pursued this quest during his AHFMR-supported post-doctoral work at the University of Pennsylvania and the University of Alberta, and he found something quite promising. He examined the central question of whether the human body activates a gene (or set of genes) in response to an HIV attack.

Amazingly, previous studies had shown that HIV infection could be stopped in human cells of a certain type, but only after these cells had been exposed to a protein called *interferon*. Interferon normally plays the role of messenger, alerting the body when a virus tries to infect it. Dr. Barr knew that interferon "turns on" certain genes that can protect the cell from HIV.

One gene in particular, however, caught his attention: *TRIM22*. In 2004, around the time Dr. Barr began his research project, a report was published

> The protein traps HIV within the cell

claiming that a gene from the rhesus monkey, when activated, could block HIV infection. This gene was called *TRIM5*. "Interestingly, the human form of *TRIM5* was ineffective against HIV. Since there are unknown risks associated with inserting a gene from another species, or even from another human being, into the body for therapy, we started thinking that maybe there's another TRIM gene that can do something similar in humans," Dr. Barr recalls. When *TRIM22* came up as one of the genes turned on by interferon, he knew where to focus his attention.

Earlier this year, Dr. Barr published his conclusions about what the protein produced by the *TRIM22* gene, TRIM22 (the protein is indicated without italics in upper case letters as TRIM22), does in a laboratory setting. "It acts by trapping HIV within the cell. This is an exciting finding because, if the virus can't get out of the cell, it would be prevented from spreading, and the onset of AIDS would be slowed or even prevented."

What's still unclear is this: If we humans have this gene, why do we get infected with HIV? Can HIV target TRIM22 and destroy it? Does something prevent the gene from being properly activated in infected individuals?

These are all questions that Dr. Barr would like to pursue in his new faculty position at the University of Western Ontario. He's optimistic that his work could lead to a new drug treatment for HIV infections. "There's still a lot more research that needs to be done but if we can figure out exactly how TRIM22 traps HIV inside cells, then we can try to develop a strategy to mimic that effect." ✻

About the researcher
Dr. Stephen Barr was an AHFMR Fellow when he completed the work described above. He is now an assistant professor of microbiology and immunology in the Schulich School of Medicine and Dentistry at the University of Western Ontario.

Selected publication
Barr SD, Smiley JR, Bushman FD. The interferon response inhibits HIV particle production by induction of TRIM22. *PloS Pathogens*. 2008 Feb;4(2):e1000007. doi:10.1371/journal.ppat.1000007.

Recommended website
The Barr Lab
http://www.uwo.ca/mni/faculty/barr/index.html

AHFMR funding partners

The Alberta Heritage Foundation for Medical Research (AHFMR) has committed more than $1 billion to Alberta's health-research community. The Foundation also relies on the contributions of many partners in building and sustaining health research in this province. In addition to AHFMR support, researchers featured in this issue of *Research News* also receive funding from the following organizations.

- Alberta Cancer Board
- Alberta Ingenuity Fund
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- Edmonton Orthopaedic ResearchTrust
- Heart and Stroke Foundation of Canada
- Howard Hughes Medical Institute
- Informatics Circle of Research Excellence (iCORE)
- Institute of Health Economics
- National Institutes of Health (NIH)
- Natural Sciences and Engineering Research Council of Canada (NSERC)
- University of Alberta Hospital Foundation

Following **up**

Where are they now?

A former AHFMR researcher's career path has led him to the other side of the world and back again.

STORY BY KATHY CLASSEN / PHOTO BY DAVID SZABO

■ Dr. Malcolm Paterson, a native of New Brunswick, originally had his sights set on a military career. However, a sports injury and the resulting hospital stay sparked an interest in medical research strong enough to set him on a different career path altogether—one that has spanned 40 years and taken him around the globe.

Dr. Paterson's international journey began with Ph.D. studies in Tennessee where he was the first foreign student to work with Dr. Richard Setlow, co-founder of the field of DNA repair. A post-doctoral fellowship took Dr. Paterson next to Holland, which laid the groundwork for his subsequent research in Ontario on DNA repair in human cells.

In 1985 Dr. Paterson was recruited to Alberta to set up a molecular oncology program at the Cross Cancer Institute in Edmonton. The establishment of the Alberta Heritage Foundation for Medical Research (AHFMR) five years earlier had contributed to an atmosphere of excitement in the biomedical research field. "AHFMR proved to be a lightning rod for both U of A and U of C in attracting world-class talent," he recalls.

Dr. Malcolm Paterson

In his research at "the Cross", he was particularly interested in environmental and hereditary factors underlying cancer. His work on genetic susceptibility to breast cancer was especially fruitful, as collaboration with Dr. Dennis Slamon at UCLA contributed to Slamon's pioneering development of Herceptin as an effective immune therapy for breast cancer.

At the end of the 1990s, an opportunity to study a group of women with a high incidence of breast cancer led Dr. Paterson to Riyadh, Saudi Arabia, where he headed a biomedical research program that featured a team of investigators from 20 nations.

The most recent bend in Dr. Paterson's career path took him to Singapore. For the past six years, he has served as the inaugural scientific director of SingHealth, a group of public-healthcare hospitals and clinics. He often found himself comparing programs he was establishing in Singapore with those AHFMR has put in place in Alberta.

"I may have left AHFMR," says Paterson, "but AHFMR has never left me. It was my good fortune to have been associated with a superb group of colleagues and trainees in those days." ❋

About the researcher
Dr. Malcolm Paterson was an *AHFMR Scientist* from 1985 to 1996. He is semi-retired and living in British Columbia.

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